ACUTE NONLYMPHOCYTIC LEUKEMIA FOLLOWING LONG-TERM ALKYLATING AGENT CHEMOTHERAPY IN THREE PATIENTS WITH OVARIAN CARCINOMA

INES MILAGROS CARRASQUILLO

1981

ACUTE NONLYMPHOCYTIC LEUKEMIA FOLLOWING LONG-TERM ALKYLATING AGENT CHEMOTHERAPY IN THREE PATIENTS WITH OVARIAN CARCINOMA

Ines Milagros Carrasquillo
B.A. Harvard University
1977

A thesis presented to the Faculty of
Yale University School of Medicine in partial
fulfillment of the requirements for the
Degree Doctor of Medicine

New Haven, Connecticut
1981

To my mother

ACKNOWLEDGEMENTS

I wish to thank Dr. Edwin Cadman and Dr. Ernest Kohorn for their guidance and assistance towards the completion of this thesis.

I also wish to express my gratitude to Dr. Howard Levitin for his advice throughout my years at Yale.

The supreme happiness of life is
the conviction that we are loved.

Victor Hugo

CONTENTS

ABBREVIATIONS

ANLL = acute nonlymphocytic leukemia
WBC = white cell count
Hgb = hemoglobin
Hct = hematocrit
UM = uracil mustard
5-FU = 5-fluorouracil
ara-C = cytosine arabinose
TZT = triazinate (dihydrofolate reductase inhibitor)

Introduction

The development of acute nonlymphocytic leukemia (ANLL) after long-term cytotoxic chemotherapy and/or radiation therapy has been reported with increasing frequency during the past 15 years. Most earlier cases were observed in patients with seemingly related hematologic disorders such as Hodgkin's disease (15), multiple myeloma (81), and polycythemia vera (110). However, reports of the development of acute leukemia among patients whose primary cancers did not involve the bone marrow and in malignancies not previously associated with the development of leukemia, such as brain (19), lung (31, 91) and breast (22) cancer, malignant melanoma (44), and ovarian carcinoma (4, 24, 26, 38, 43, 46, 112, 89, 48, 57, 63, 66, 36, 67, 70, 73, 76, 85) were disturbing. In all these cases the primary mode of treatment involved single or multiple agent chemotherapy and/or radiation therapy.

The development of ANLL in these patients has led to the speculation that this condition is a post-therapeutic complication of the intensive therapy administered, rather than an end development of the natural history of the initial malignancy. Reports of ANLL developing in chronically immunosuppressed patients treated with cytotoxic agents for connective tissue diseases (19, 79, 70), in renal transplantation patients (41) and other non-neoplastic diseases (96, 50, 75, 68, 111) further supports this view.

Although radiation therapy has been associated with leukemogenesis, chemotherapy with alkylating agents appears to carry a higher risk of development of ANLL than is otherwise expected. The mechanism of action of these drugs at the cellular level is thought to resemble

that of irradiation, which has been proven to be a potent leukemogen.

Alkylating agents have proved particularly effective in the treatment of ovarian cancer and have been used more extensively in the management of this disease than any other agents. Therefore, ovarian cancer patients would appear to incur a particularly high risk of post-therapeutic acute leukemia.

Materials and Methods

Between 1964 and 1971, 79 patients with ovarian carcinoma were treated at Yale-New Haven Hospital with a combination of surgery, radiotherapy, and chemotherapy. Tumors were staged and classified according to the guidelines of the International Federation of Gynecology and Obstetrics (see Table 1). Uracil mustard, an alkylating agent, and 5-fluorouracil (5-FU), a pyrimidine antimetabolite, were chosen as chemotherapeutic agents because of their proven synergistic activity against various neoplasms in laboratory studies with mice. The protocol at that time consisted of 1 mg/kg/day of uracil mustard as a continual oral dose and 5-FU at a dose of 5 mg/kg intravenously for 5 days, every 4 weeks. Hematologic toxicity was followed with weekly white blood cell counts (WBC) with differential, hemoglobin levels, hematocrit levels and platelet counts. If leukopenia or thrombocytopenia developed, as evidenced by a WBC lower than $4{,}000/mm^3$ or a platelet count lower than $100{,}000/mm^3$, the chemotherapy was discontinued until these signs of bone marrow function improved. Anemia was treated with oral iron medication and blood transfusions if necessary. Therapy was also discontinued during any infectious processes. The patients' progress was assessed in the gynecological chemotherapy clinic by physical examination and laboratory studies which included liver function tests, blood urea nitrogen and creatinine, haptoglobin levels, and chest X-rays, if indicated.

An objective response was defined as a complete disappearance of the tumor mass as measured by inspection, palpation, or roentgenography, and a disappearance of ascites, both sustained for a three

month period during which no new tumor lesions developed. A partial response consisted of a decrease in the size of the tumor over a 3 month period or control of serous effusions for 3 months or longer. A nonresponse was defined as failure to effect a response on the basis of the therapy administered according to the planned regimen during at least a three-month period.

In this group of 79 patients, 16 responders survived longer than 36 months, and of these, three developed ANLL. Two patients received multiple courses of anti-leukemic chemotherapy, but a remission was not obtained in either patient. Patient 1 was treated with various combinations of methotrexate, leukovorin, doxorubiun, cyclophosphamide, vincristine, ara-C, 6-mercaptopurine, azauridine, TZT, and pyrazofurin. Patient 2 was treated with daunomycin and ara-C. The third patient received only palliative treatment for pancytopenias and infections.

Case reports of these three patients follow.

PATIENT 1

Mrs. A.S. was a nulliparous 48 year old white female, with a history of menometrorrhagia since 1951. Between 1964 and 1969 she had been treated with birth control pills. In June, 1969, the patient developed continuous vaginal bleeding with heavy clots and lower abdominal pains. Pelvic examination showed a uterus twice normal size and a mass in the left adnexa measuring about 10 cm. in diameter. The right adnexa was unremarkable. In October, 1969, an endometrial biopsy showed adenomatous hyperplasia. An intravenous pyelogram showed a rounded soft tissue mass in the left pelvis pressing on the bladder. On November 10, 1969, she underwent exploratory laparotomy.

The uterus appeared normal. The left ovary was found to be replaced by a multilocular cystic mass measuring 8.5 x 10 cm. The right ovary was also multiloculated and filled with chocolate-colored fluid. There were no ascites or implants in the peritoneal cavity. The omentum was normal and there was no evidence of liver metastases. Histologic examination of the left mass by frozen section showed a papillary adenocarcinoma of the ovary. A total abdominal hysterectomy and bilateral-salpingo-oophorectomy were performed. The pathology report confirmed the diagnosis of ovarian carcinoma grade 1 and also showed an invasive adenocarcinoma of the endometrium. The ovarian cancer involved the left ovary and the left fallopian tube; the right ovary was free of disease. The tumor was thus a stage IIA papillary adeno-carcinoma of the ovary; the endometrial cancer was stage IA, grade 1.

Following recovery from the surgery, the patient was treated with radiation therapy. She received 1,200 rads to the whole abdomen and an additional 2,800 rads to the pelvis between November 19 and December 22. This course of therapy was complicated by severe diarrhea, treated with Lomotil, and by a dry desquamation of the skin of the abdomen and the posterior buttocks, which resolved upon cessation of therapy. Subsequent pelvic examination showed no evidence of either abdominal or pelvic masses. On January 14, 1970, a radium plaque with a total dose of 1,200 mgm hours was inserted vaginally for 33 hours to prevent vaginal vault recurrence of the endometrial cancer.

In February, 1970, the patient developed ascites and a diagnostic paracentesis was performed. Analysis of the fluid showed malignant cells consistent with adenocarcinoma. In March the patient was started

on chemotherapy with a combination of uracil mustard and 5-fluorouracil, and also with Depo-Provera, 400 mg. per week by intramuscular injection. During each five day course of 5-FU, the patient had diarrhea, which resolved after treatment. In October, 1970, pelvic examination revealed a 6 cm. mass at the apex of the vagina. However, this had regressed entirely by August, 1971, and the patient remained asymptomatic and free of disease for the remainder of treatment.

In May, 1971, she developed a mild pancytopenia with a macrocytic anemia, Vitamin B12 and red cell folate levels were depressed. The WBC was 4,100 cells/mm^3 with a normal differential; the Hgb was 9.8 gm/dl, the Hct was 31.2%, and the platelet count was 80,000/mm^3. A work-up for a malabsorption syndrome was negative. Treatment with Vitamin B12, iron, Vitamin C, and multi-vitamins was begun, with improvement of the macrocytosis, but mild anemia persisted with the Hgb levels fluctuating between 11.7 and 13.0 gm/dl.

Chemotherapy was continued uninterrupted for 33 months until December, 1972. The total dose of uracil mustard was 900 mgs. and that of 5-FU was 71 gms. At the end of therapy the WBC was 4,500/mm^3 with a normal differential; the Hgb was 11.7 gm/dl, the Hct was 36.7%, and the platelet count was 150,000/mm^3. The patient was in good health without evidence of recurrence of either the ovarian or endometrial cancers; however she was lost to follow-up.

In November, 1974, 23 months after completing chemotherapy, Mrs. S. experienced increasing shortness of breath, developed a cough with a white sputum, and had occasional chills. On physical examination she had a 0.4 cm. ulcerated lesion of the left chin. There were no

petechiae, purpura, lymphadenopathy, or pedal edema. The spleen was not palpable. The WBC was 50,600 cells/mm^3 with 35% blasts. The Hgb was 9.5 gm/dl, the Hct was 35%, and the platelet count was 975,000/mm^3. She was admitted to Yale-New Haven Hospital for investigation with a provisional diagnosis of leukemia.

Bone marrow aspirate showed a hypercellular marrow with 17% myeloid cells, 24% erythroid cells, and 45% myeloblasts. The erythroid elements showed a predominance of early basophilic forms with vacuolization, binucleation, nuclear hyperlobulation, and megaloblastic forms. The myeloid:erythroid ratio was 1:1. A chromosomal study revealed a female karyotype with 45 chromosomes. All cells examined were abnormal, with chromosome no. 18 missing. The long arm of chromosome no. 3 contained extra material which may have been the result of a translocation of some of chromosome no. 18. There was no Ph^1 chromosome. A diagnosis of acute myelogenous leukemia was made.

On November 25 antileukemia therapy with multiple agents was begun. There was never a remission and she expired six months later. At autopsy, the gastrointestinal tract exhibited multiple ulcerations. The liver and spleen were severely congested and were extensively involved with leukemic cells. The bone marrow was hypercellular, with marked hyperplasia of the myeloid series, mostly myeloblasts. There was no sign of recurrent ovarian disease.

PATIENT 2

Mrs. J.J. was a 43 year old nulliparous black female, who had had a history of occasional dysmenorrhea and lower abdominal pain since 1966. On physical examination in August 1969, an enlarged,

irregular uterus and a large right adnexal cystic mass were palpated. The left adnexa was unremarkable. A diagnosis of uterine leiomyoma was made, and upon an increase in the severity of symptoms, the patient was admitted to Yale-New Haven Hospital in November, 1969, for dilatation and curettage, pelvic examination under anesthesia and possible abdominal hysterectomy.

On November 12, examination under anesthesia showed a right ovary approximately three times normal size; the left ovary could not be palpated, and the uterus was enlarged with a possible fibroid. An exploratory laparotomy was performed. Upon entering the abdominal cavity, a large amount of blood-stained fluid was found; the omentum was edematous, thickened, and somewhat nodular, although no definite metastatic nodules were discovered. The right ovary was surrounded by a large fungating mass which spread posteriorly to involve the posterior surface of the uterus and the cul-de-sac; the left ovary was enlarged and was covered with a fungating mass. The liver could not be palpated because of adhesions in the right upper quadrant. The para-aortic nodes were not enlarged. A biopsy of the right ovary was taken, and the abdomen was closed without further resection. The pathology report showed a low grade papillary serous cystadenocarcinoma.

Between November 24 and December 30 the patient received 2,000 rads to the whole abdomen and an additional 1,800 rads to the pelvis. Initially she tolerated the treatment well, but in mid-December increasing abdominal pain developed and she became anemic. The pelvic mass, which previously was barely palpable abdominally, now showed a rapid increase in size, filling the entire lower abdomen and rising up to

about two finger breadths above the umbilicus. Mrs. J. was seen in the emergency room several times in late December because of lower abdominal pain and treated with analgesics. On December 31, she was admitted to the hospital for investigation. An intravenous pyelogram showed a soft tissue mass in the pelvis and bilateral partial obstruction of the ureters. She was discharged January 7 and readmitted on January 28, complaining of anorexia, increased abdominal pain and fever. Intermittent episodes of diarrhea began on this admission and resolved with Lomotil. In February the patient developed a *Klebsiella* sepsis. Chest X-ray on February 14 showed a left lower lobe pneumonia with atelectasis and a left pleural effusion. Treatment with Gentamycin resulted in improvement.

A three-way abdominal film also taken on the 14th showed multiple air fluid levels in the large and small bowel. These findings were believed to be evidence of either a paralytic ileus secondary to abdominal carcinomatosis or a distal large bowel obstruction.

On February 27, the patient underwent a second exploratory laparotomy. Examination of the abdominal cavity revealed two large ovarian masses adherent to loops of the small bowel and the sigmoid colon, all of which were adherent anteriorly to the bladder. The right ovary measured 8 x 4 cm.; the left ovary was 5.5 cm. in diameter. A bilateral salpingo-oophorectomy and subtotal omentectomy were performed. However, remnants of tumor were left on the sigmoid colon, near the area of the cecum on the right, and between the uterus and the bladder anteriorly; these were all clipped. Minimal nodularity was noted in the cul-de-sac on the back of the uterus. Histologic examination

confirmed the previous diagnosis of papillary serous cystadenocarcinoma of the ovary (Stage III). Postoperatively, Mrs. J. did well except for brief episodes of diarrhea, which resolved spontaneously.

Chemotherapy for the nonresectable disease was begun on April 6, 1970, with a combination of uracil mustard and 5-fluorouracil. The WBC was 8,700 cell/mm^3 with a normal differential, the Hgb was 8.5 gm/dl, and the platelet count was 80,000/mm^2. In October, a pelvic examination was remarkable in revealing an irregular, firm, mobile, 3 cm. mass to the right of the uterus, however, by December the mass had regressed entirely. Therapy was complicated by the onset of constant diarrhea, with up to 6 bowel movements per day. Sigmoidoscopy and a barium enema revealed extensive colitis as a consequence of the original radiation therapy. The diarrhea was successfully treated with Paregoric and Lomotil. At the same time the patient's hematocrit decreased to 21%, and she received three units of PRBC. On July 6, she had another episode of anemia with a Hct of 19% and received two units of PRBC. She tolerated the remainder of the chemotherapy for the ovarian cancer well without any other somatic complaints or severe hematologic abnormalities.

All subsequent examinations, liver studies, and intravenous pyelograms showed no evidence of recurrent disease. The patient refused second-look surgery. Therapy continued with only brief interruptions until June, 1975, after 62 months; a total dosage of uracil mustard 1,700 mgs. and 5-fluorouracil 85.8 gms. had been administered. At this time, the WBC was 4,500/mm^3 with a normal differential count. The Hgb was 10.3 gm/dl, the Hct was 32.3%, and the platelet count was

$170,000/mm^3$. Mrs. J. was active and in good health during the following 17 months, but was lost to follow-up at the end of this period.

In October, 1976, she began to complain of bleeding of the gums. Routine hematologic studies in November showed that the WBC was $5,800/mm^3$ with 8% blasts; the Hct was 26% and the platelet count was $31,000/mm^3$. Physical examination was remarkable for ecchymoses over the legs and petechiae over the ankles. The spleen was slightly enlarged with no lymphadenopathy. Bone marrow aspirate revealed a 4+ cellular marrow with 50% blasts that had monocytoid features, and 35% erythroid elements, 15% of which were early precursors, showing marked atypia of development with megaloblastic changes and many binucleated and trinucleated forms. The myeloid:erythroid ratio was 5:3. A diagnosis of acute myelomonoblastic leukemia with a marked dyserythropoiesis was made. The patient was admitted for treatment on November 4th and received three courses of chemotherapy with daunomycin and ara-C without benefit. She expired six months later. An autopsy was not performed. There had been no clinical evidence of recurrent ovarian cancer.

PATIENT 3

Mrs. J.M. was a 51 year old white female, gravida 2, para 2, with a history of recurrent lower abdominal pain beginning September, 1969 and a tentative diagnosis of diverticulitis. On January 12, 1970, she noticed right lower abdominal swelling. She was admitted to Widham Community Memorial Hospital in Connecticut for evaluation. On physical examination there was a definite, non-tender, cystic mass in the right lower quadrant. Pelvic examination showed a fullness in

the anterior vaginal vault. Ballotment of the cervix was associated with anterior motion of the entire mass. An abdominal film showed a large pelvic mass. A barium enema was negative for diverticulitis and showed that the mass did not involve the colon. On January 15, the patient underwent sigmoidoscopy, pelvic examination under anesthesia, and dilatation and curettage.

On January 19, an exploratory laparotomy was performed. A large mass, replacing the right ovary and involving the right fallopian tube, the left fallopian tube, and the left ovary was found. Implants of tumor covered the gastrointestinal tract, which was adherent to the pelvis. A total abdominal hysterectomy and bilateral salpingo-oophorectomy were performed. Histology showed an adenocarcinoma of the ovary with both glandular and squamous elements, consistent with the endometroid pattern of ovarian cancer. A diagnosis of stage III adenocarcinoma of the ovary was made.

After a slow and uneventful recovery, the patient received radiotherapy for the residual cancer. Between March 2 and April 4, 1970, 2,000 rads were administered to the whole abdomen and an additional 1,875 rads to the pelvis. She tolerated the treatment well except for several thrombocytopenic and leukopenic episodes which were resolved by brief cessations of therapy. The patient also experienced mild nausea and diarrhea, which was successfully treated with Compazine and Lomotil. Physical and pelvic examinations at the end of treatment were negative for tumor.

On August 24, an ill-defined mass in the right mid-abdomen was palpated abdominally, but not on pelvic examination. This was assumed

to be a recurrence of the ovarian carcinoma, and the patient was started on chemotherapy.

As with the previous two patients, Mrs. M. received 5-fluorouracil for five consecutive days each month, but uracil mustard was administered at a dosage of 1 mg. every other day, instead of 1 mg. every day because of frequent leukopenic episodes. By March, 1971, there was no evidence of the abdominal mass, and the patient remained free of recurrent disease. In September, 1971, leukopenia developed and the dose of uracil mustard was changed to 1 mg. every third day. The leukopenia persisted and thrombocytopenia developed and all therapy was discontinued in April, 1973. Total treatment time was 32 months, with a total uracil mustard dose of 348 mgs. and 5-FU a total dose of 24 gms.

The patient was in excellent health for the next four and a half years, although she had persistent anemia and a slight leukopenia. The WBC was 4,200/mm^3, with a normal differential; the Hct was 35% and the platelet count was within normal limits. In late December, 1977, the patient began to experience mild dyspneic episodes while walking. A routine hematologic study revealed a pancytopenia: the WBC was 1,900/mm^3, the Hct was 27.7% and the platelet count was 120,000/mm^3. A bone marrow aspirate in January showed a markedly hypocellular marrow with 50% blasts and 20% lymphoblasts. There were a few scattered erythroid precursors which exhibited megaloblastic changes. This was compatible with a myelodysplastic syndrome or an evolving acute myeloblastic leukemia; however, because of her age and her previous history of radiotherapy and long-term chemotherapy, the patient was

followed closely and treated symptomatically with intermittent red blood cell and platelet transfusions rather than receiving more aggressive treatment. A chromosome analysis showed a normal karyotype.

During the next five months, there was a slow progression of her disease. She became increasingly more symptomatic as evidenced by fatigue, pallor, bony pain, and small, sporadic ecchymoses. The bone marrow remained severely hypocellular, and the patient became increasingly dependent on platelet transfusions. There was a slow, progressive development of her myeloblastic leukemia into an acute monocytic type by the end of March. The patient died June 1978 after being lost to follow-up. An autopsy was not performed but at the last physical examination she was thought to be free of recurrent ovarian disease.

Results

In this group of 79 patients treated for advanced ovarian cancer, 16 (20.25%) survived more than three years after their initial diagnosis. Eight of these died of recurrent disease at 39, 41, 48, 51, 68, 96, 105 and 108 months respectively. Two patients died of coronary artery thrombosis at 84 and 120 months. A third died of unknown causes at age 83 after a survival of 96 months. She had a laparotomy at age 80 and she was free of ovarian cancer. Two patients are alive 120 and 156 months after diagnosis; one of these had a stage IIB carcinoma of the ovary, the other a stage III carcinoma of low grade. The remaining three patients (18.75%) developed ANLL 56, 79, and 84 months after chemotherapy was started. These three patients represent 3.75% of the total group undergoing treatment; a significant percentage

when compared to the number of expected cases of ANLL in the general population which is 2.2 cases per 100,000 (99).

All 16 patients were initially treated surgically, then received radiation therapy and chemotherapy with uracil mustard and 5-FU; three patients were unresponsive to these agents and received chlorambucil and vinblastine. The development of acute leukemia was not related to the cumulative dose of uracil mustard administered (see Table 2), as all three patients appeared to be evenly distributed within a dose range of 348 mgs. and 1700 mgs.

Among the three patients who developed leukemia only the first appeared to have disease amenable to optimal surgical resection; the other two had widely disseminated unresectable disease at the time of diagnosis. All three received radiation therapy to the abdomen and pelvis and in addition the first patient received radium therapy. Radiation doses ranged from 3800R to 4000R. Episodes of cytopenia were common during the course of this treatment, with the development of thrombocytopenia in patient 1, anemia in patient 2, and both leukopenia and thrombocytopenia in patient 3. However, all abnormalities were rapidly reversible with brief cessations of therapy. Exposure to radiation did not appear to influence the interval prior to leukemia development; all three received almost identical doses.

Chemotherapy with uracil mustard and 5-FU was begun for the treatment of unresectable disease and was maintained for a period ranging from 32 to 62 months (mean 42.3 months). The total dose of uracil mustard ranged from 348 mgs. to 1700 mgs.; and the total dose of 5-FU ranged from 24 gms. to 85.5 gms. Episodes of cytopenias

occurred in all three patients throughout treatment although none developed pancytopenia. In the first two cases cessation of therapy brought about resolution of these abnormalities but in the third case leukopenic episodes were frequent and persistent despite adjustment of the dose of uracil mustard. A lack of objective evidence of recurrent disease in all patients and the onset of persistent leukopenia and thrombocytopenia in the third patient led to discontinuation of therapy. Second-look laparotomies were not performed.

ANLL developed after a latent period of 56, 79, and 86 months respectively (mean 73.6 months). The first patient had normal hematologic parameters during the time she maintained follow-up. She presented with leukocytosis, and increased platelet count, and a mild anemia. A chromosomal study showed hypodipoidy. She received intensive anti-leukemic therapy with multiple agents but was unresponsive. A preleukemic syndrome also appeared to be absent in the second patient. She presented with anemia, thrombocytopenia, and a normal WBC. This patient had the shortest latent period and received the largest dose of uracil mustard. A chromosomal study was not performed. She underwent three unsuccessful attempts at induction of a remission. Bone marrow studies in these two cases showed similar patterns. Both were highly hypercellular with bizarre, immature granulocytic forms and megaloblastoid changes. Megakaryocytes were abnormal and severely depleted. There was marked dyserythropoiesis with rare mature erythroid elements, many erythroblasts, and ringed sideroblasts. Death occurred five and seven months after leukemia developed, respectively. At autopsy the first patient was free of ovarian cancer; the second

had no evidence of disease at the last physical examination.

The third patient developed a persistent anemia 13 months prior to the onset of acute leukemia although she did not become pancytopenic until 1 month before diagnosis. This patient received the lowest dose of uracil mustard and had the longest latent period. However, she experienced the greatest amount of marrow damage as evidenced by persistent leukopenia throughout treatment and by the history of anemia before the onset of leukemia. A chromosomal study showed a normal karyotype. Initial bone marrow analysis showed severe hypocellularity and erythroid hypoplasia consistent with a myelodysplastic syndrome, but without enough cellular differentiation to establish an accurate diagnosis. Over the next three months more definite changes in the marrow consistent with acute myelogenous leukemia began to appear, until finally all abnormalities were consistent with the diagnosis of acute myelomonocytic leukemia. This patient did not receive antileukemic therapy. Death occurred seven months after the diagnosis of leukemia. An autopsy was not performed, but at the last physical examination there was no evidence of recurrent carcinoma.

Literature Review

The earliest report of the development of acute leukemia in a patient with ovarian cancer appeared in 1962. The patient was one of 14 with a primary malignancy that was treated with extensive radiation therapy, and who developed leukemia following a long disease-free interval (26).

Reports implicating alkylating agents in the development of acute leukemia following therapy for ovarian cancer began appearing in 1970. To date a total of 54 patients (including the three presented here), have been reported (see Table 2). Of these, 26 were staged at the time of diagnosis: 2 presented in stage IV disease, 18 in stage III, 2 in stage IIA, and one each in stages Ia, Ib, and Ic. Of the remaining 28, five were reported to have disease outside the pelvis at the time of surgery although they were not staged; in 23 this information was not provided although the case histories were consistent with advanced disease.

Twenty-four patients (44.44%) did not receive radiation therapy. They were treated with one or more alkylating agents or with one alkylating agent and an antimetabolite. The duration of therapy in this group ranged from 4 months to 90 months. The most frequent single agents used were melphalan (phenylalanine mustard) (11 patients), leukeran (chlorambucil) (9 patients), treosulfan (8 patients), thiotepa (3 patients), and cytoxan (cyclophospamide) (1 patient). The two non-alkylating agents used were: methotrexate and 5-FU. Six patients were treated with a combination of uracil mustard and 5-FU; nine others received various combinations of the above agents. Thus, the

leukemogenic affect of irradiation cannot explain the development of ANLL in almost half of the patients who received prolonged cytotoxic agent therapy.

In addition to chemotherapy, twenty-four patients (44.44%) received radiation therapy which consisted of irradiating the whole abdomen and/or the pelvis, radium treatments or ^{32}P therapy. Two patients (3.70%) received irradiation only. Three patients received chemotherapy but a history of radiation therapy was not documented. In one patient therapy was not specified. Although the relative significance of irradiation in these patients was not closely analyzed, in two groups of patients it did not appear to be a major leukemogenic factor. In the report by Reimer et al, all 13 cases of ANLL developed in the group treated with chemotherapy (76). In the report by Pedersen-Bjegaard et al, of 553 patients treated for ovarian cancer, 274 received radiation therapy and only 2 of these developed ANLL in contrast to five patients in the remaining 279 patients treated with chemotherapy. However, these two patients had the shortest latent period from the initiation of chemotherapy to the development of leukemia (67).

Three patients (76, 111) were treated with surgery, radiation therapy and chemotherapy with uracil mustard and 5-FU. The duration of therapy and total dose received were not reported. In the first patient a detailed history was not provided. The latent periods were 26, 60 and 84 months respectively (mean 56.6 months). The second and third patient were pancytopenic for an undetermined period of time before the diagnosis of ANLL. A chromosomal study in the second patient was abnormal showing hypodiploidy. These two patients received

antileukemic therapy and achieved partial remission. Survival after the diagnosis of leukemia was 6 and 7 months, and considerably longer than other patients with ANLL. The cause of death was not reported, but at autopsy there was no evidence of either leukemia or ovarian carcinoma.

Eight patients underwent a second laparotomy at some point during their treatment; two of these were necessary to relieve an ileus (89) and a small bowel obstruction (48), and six were diagnostic second look procedures (24, 63, 76). In the two cases where surgery was required, the first patient had not received chemotherapy for the previous 16 months because an earlier negative laparotomy performed to relieve an ileus was negative for ovarian tumor. At the time of the second surgery she was found to have widespread disease and was re-started on chemotherapy. In the second patient, the obstruction was secondary to adhesions. Although there was no evidence of cancer at the time of the operation, the patient was restarted on chemotherapy six months later. Of the six patients who underwent elective surgery, all were free of disease; in three chemotherapy was discontinued.

The clinical course of secondary ANLL in most patients was often preceded by frequent episodes of pancytopenias and cytopenias (97.7%). Hematologic abnormalities developed in 42 patients prior to the development of leukemia. Thirty-five were pancytopenic for a period ranging from one to 36 months. Seven experienced varying degrees of cytopenias but did not develop pancytopenia. In 11 patients this information was not provided. All attempts at treatment with testos-terone and corticosteroids were unsuccessful. These symptoms have

been previously reported to be characteristic of preleukemic states (44, 15, 81).

The latent period from the beginning of chemotherapy to the diagnosis of ANLL ranged from 19 months to 114 months, with a mean of 52.8 months. This interval was slightly longer for those patients who received chemotherapy only (mean 55.6 months), as opposed to those who received both chemotherapy and radiation therapy (mean 52.1 months). A latent time of four to five years after the start of chemotherapy corresponds closely to the findings in other series of patients with ovarian cancer (67, 76), lung cancer (95), multiple myeloma (79) and Hodgkin's disease (80) who have developed ANLL.

Acute myeloid leukemia was the most common type of leukemia (26 cases), followed by acute myelomonocytic and erythroleukemia which developed with equal frequency (eight cases each). One patient presented with a myeloproliferative syndrome which later developed into erythroleukemia; another presented with a myelodysplastic syndrome which later developed into acute myeloid and then into acute myelomonocytic leukemia. There was one case of acute undifferentiated leukemia.

Chromosome analysis was reported in 12 cases. Nine of these were abnormal, with hypodiploidy the most common aberration. Three karyotypes were normal (36, patient 54, Table 2). These three patients presented with a preleukemic syndrome. These cytogenetic studies are consistent with previous reports of a very high incidence of karyotype abnormalities in secondary ANLL (15, 67, 80).

Bone marrow findings were similar in most patients. The majority

were markedly hypercellular, although a few were hypocellular and two patients had myelofibrosis. There was a predominance of myeloblasts, promyelocytes, or myelomonocytes, with a severe left shift in myelocytic differentiation. Dyserythropoiesis was a common finding with hyperplasia and megaloblastoid changes of the erythroid elements. Ringed sideroblasts were usually present.

Secondary ANLL seems to a great extent to be refractory to therapy, both in patients with previous ovarian cancer and in patients with other primary tumors. Only a few brief remissions have been described (15, 36, 57, 67, 81, 92). However, in most of these cases, the antileukemic therapy administered was insufficient for treatment of ANLL due to initial diagnostic problems in some patients and to the rapid course of the disease in others (67). Of the 27 patients treated, only three achieved complete remission (63, 112), four had partial remissions (48, 73, 112), and two were unresponsive but alive with progressive disease at one and two months after diagnosis (67). Twenty-two patients were not treated; two were alive at one month and seven months after diagnosis. In four patients the course after diagnosis was not reported.

Post-mortem examinations were performed in 32 patients. Thirty had extensive dissemination of leukemia; 22 of these were free of ovarian disease. Of those not autopsied, four had no clinical evidence of disease at the time of the last physical examination; five were alive at the time of report and were free of ovarian disease.

Ovarian Cancer Management

Ovarian carcinoma, though taking second place to endometrial carcinoma in frequency, remains the one gynecologic malignancy frequently not amenable to successful therapy. The therapeutic management of this disease has changed greatly in the last 20 years. The most significant factor was the realization that effective treatment required precise and accurate staging. Such staging can only be done by adequate exploration of the whole abdominal cavity, particularly the surface of the liver, the undersurfaces of the diaphragm, the paracolic gutters and the retroperitoneal nodes. Prior to 1965 these regions were frequently not explored and the extent of the disease was underestimated. The routine use of omentectomy also led to more accurate staging as the cancer frequently showed microscopic or small nodular involvement of the omentum. Such understaging explained the frequently found poor prognosis of apparently early disease.

Concurrently with more accurate staging came the realization that patients with bulk disease remaining after surgery responded poorly to postoperative radiation. The chemotherapy agents used in the leukemias and lymphomas began to be used in solid tumors and patients with ovarian carcinoma were found to show response (104A). This led to clinical trials using alkylating agents in ovarian carcinoma. Phenylalanine mustard at M.D. Anderson, cytoxan at the Mayo clinic, and chlorambucil in London and New York were found to have very similar response rates. Palliation in advanced disease was shown to be possible and although little prolongation of life was achieved, tumor masses decreased in size and serous effusions resolved, frequently for many months.

Concurrently with the introduction of chemotherapy and the realization of the prognostic significance of bulk tumor, came the treatment practice of removing as much tumor as possible, a debulking procedure. All possible tumor is removed by oophorectomy, hysterectomy, omentectomy, and if necessary bowel resection so that the least possible amount of tumor is left to be treated by the chemotherapy (12A). Because patients who have all disease removed or who have only minimal disease left do better and live longer than those in whom bulk disease is left, the procedure of surgical debulking has become standard practice.

It was against the background of the use of single agent chemotherapy that the use of uracil mustard and 5-FU (UMFU) was introduced in 1964 as one of the first combination regimens in ovarian cancer. Combination drugs appeared to be more effective in lymphoid neoplasms and Booth and Sartorelli (11) had demonstrated a synergism between these agents in experimental sarcomas.

UMFU had provided a response rate similar to alkylating single agent chemotherapy but no prolonged survival in the dose regimen used. There is no record of uracil mustard having been tried as a single agent in ovarian carcinoma, particularly with an intermittent dose schedule.

The trial continued until 1970. At that time adriamycin became available and its use in combination with cytoxan and other agents appeared more promising than UMFU. Since then, platinum, hexamethylmelamine, and adriamycin in combination with alkylating agents have superceded this early attempt at combination chemotherapy.

Discussion

The incidence of acute granulocytic leukemia and its variants in the general population in the United States has been shown to be 2.2 cases per 100,000 persons per year (99). Since the advent of intensive therapy, the development of ANLL in ovarian carcinoma has been shown to be occurring with greater than expected frequency. Estimates of the actual frequency in these patients is not yet possible because of the relatively small number of case reports (17).

It was initially thought that the increased complication of secondary ANLL after treatment for a different primary malignancy was a consequence of the increased numbers of long-term survivors that resulted from successful therapy (36, 112); prolonged survival in these patients unmasking a natural tendency to develop another malignancy (46). The development of acute leukemia in hematologic disorders which originally involved the bone marrow, such as multiple myeloma, Hodgkin's disease, Waldenstrom's macroglobulenemia, and chronic lymphocytic leukemia lent evidence to the suspicion that acute leukemia may have been a natural, although late manifestation of these disorders, rare until a few years ago (44, 15, 98). However, the appearance of ANLL in patients with solid tumors and in immunosuppressed patients made this supposition unlikely (17). Specifically, the association of ovarian carcinoma and acute leukemia is very rare (43). This disease has not been known to evolve as part of the natural history of ovarian cancer and epidemiologic studies have not suggested any special association between the two (76).

In the most comprehensive series to date of patients with ANLL

following ovarian cancer, Reimer et al could not demonstrate an increased incidence of acute leukemia in a historical control group. These patients had ovarian cancer which was treated between the years 1935 and 1972. The authors concluded that there was no evidence of an "inherent" risk of leukemia in patients with ovarian disease (76). The question also arises that the leukemia may be a part of the natural history of the disease, specifically associated with advanced cases. However, although the majority of patients who have received intensive therapy have had advanced widespread disease, the patients in the Reimer study were presumed to be in the early stages (76). In addition three cases of ANLL were reported by Pederson-Bjergaard et al in patients with Stage I disease (67); two other patients (24, and one of the present cases - No. 52) were in stage IIA. The possibility of a chance association cannot be ignored, however, there is mounting evidence that suggests a relationship exists between the use of cytotoxic drugs and the development of leukemia in these patients.

It is known that these agents, while allowing control of the primary cancer, may permit or induce the growth of a second malignancy. As patients with ovarian carcinoma survive longer or are cured by the use of radiation and/or chemotherapy, the long-term complications of these methods of therapy may become more evident (17, 81). Further association between therapy and the development of ANLL can be seen in five earlier reports in addition to the present three cases (see Table 4). While the patients who developed leukemia in these reports represented a small fraction of the total sample of those undergoing treatment, they represented a significant percentage of

the long-term survivors. The most significant numbers appear among the three patients reported here who represent more than 3% of the total treated group, and 18.75% of the long-term survivors. In the report by Reimer et al, the 13 patients with leukemia represented 0.75% of the total sample, however, they showed a 36-fold increase in the incidence of secondary acute leukemia (13 cases observed compared with a theoretically predicted number of 0.36) compared with the general population (76). In the population followed by Pederson-Bjergaard, et al, the expected number of cases of acute leukemia was 0.004, they observed 7, a relative risk of 175 (67).

A suspected dose effect relationship could not be confirmed in any of the previous studies, but in an earlier study by Einhorn leukemia developed in 4 of the 12 patients who received 800 mg. of melphalan (24). Only in the treatment of Hodgkin's disease has it been shown that the risk of developing leukemia is a function of the intensity of therapy administered (44, 15). This risk is maximal when extensive irradiation is combined with polychemotherapy, the frequency of post-therapeutic leukemia being 29 times that of the general population (44, 15). Therefore, it would seem that aggressiveness of therapy is an important factor in the development of ANLL although the exact relationship between dose and leukemia has not been clarified.

The role of radiation therapy in this group of patients has yet to be defined. Irradiation has been suspect as a leukemogenic agent since 1925, when reports associating an increased incidence of acute leukemia in radiologists routinely exposed to radiation began to appear

(101). The literature contains at least two dozen patients described in detail who have developed ANLL following treatment with radiation only, including patients who were treated with localized therapy (17, 72).

Studies on leukemia incidence and chromosomal analysis in humans after accidental, diagnostic, or therapeutic exposure to irradiation provided solid evidence that among these patients the risk of developing leukemia was higher than in the rest of the population (10, 51). Data collected by the Atomic Bomb Casualty Commission show an increase in the incidence of leukemia in Japanese atomic bomb survivors in Hiroshima and Nagasaki (8, 9, 62). Studies of children exposed to radiation prenatally, for treatment of childhood carcinoma or during therapy for thymic enlargement and other medical ailments which were routinely treated with irradiation show that the number of deaths from leukemia exceeds that expected to occur in untreated children by a factor of 10 (55, 64, 88). Similarly, patients suffering from ankylosing spondylitis who were treated with multiple courses of localized radiation to the spinal column, and patients with polycythemia vera treated with radiation and ^{32}P have a higher incidence of leukemia, up to 10 times that of untreated patients (13, 21, 61).

Numerous other forms of cancer or benign disorders have been treated by radiotherapy alone (44). Several cases of secondary leukemia in these patients have been reported, occurring in four cases of Wilm's tumor (83), one cancer of the tongue (72), five cases of cancer of the larynx (45); all these patients had received local radiotherapy of up to 3,000 rads; in seven cases the acute leukemia

was myeloblastic and three others lymphoblastic. Survival was always less than six months (44). In a study of pelvic irradiation, Smith documented 34 cases of acute leukemia (against a theoretically predicted number of 33) out of 110,000 cervical cancers treated locally by radium or by local radiotherapy (doses of 1200 to 1500 rads.) In contrast, in the same study, out of more than 8,000 women in whom menopause was induced by radiotherapy, (a dose of 70 to 190 rads to the entire pelvis), 33 cases of acute leukemia developed while the theoretically predicted number was 13.5, an almost three-fold increase over the calculated incidence (90).

Radiotherapy appears to intervene in the leukemogenic process more by virtue of the extent of the irradiation than by the total dose delivered, since irradiation of the pelvis with less than 200 rads multiplies by a factor of 3 the risk of acute leukemia, while 300 to 1500 rads to the cervix does not increase the frequency (44). The same is found in Hodgkin's disease, where extensive irradiation increases the incidence of post-therapeutic acute leukemia (15).

In some of these series, ANLL developed only after intensive combined chemotherapy and radiotherapy, suggesting an additive effect of the two modalities of treatment. It is probable that the combination of radiation therapy and alkylating agent chemotherapy is more leukemogenic than either mode of therapy alone.

Alkylating components are known to be immunosuppressive, leukemogenic, and carcinogenic in experimental animals and may exhibit these same characteristics in man (37, 65, 84, 86, 108). They probably exert their principal effects by accentuating immunosuppression and generating

chromosomal damage, as animal studies with melphalan have demonstrated (109).

The first clear evidence that the alkylating agents are leukemogenic has been provided by the accumulating case reports of the development of leukemia after therapy with these drugs. The multiplicity of drugs associated with secondary ANLL may suggest that any cytotoxic agent may be capable of leukemogenesis, however, the major conclusive evidence lies on the alkylating agents as a group since these drugs account for more than 85% of all reported cases. While cases of ANLL have followed therapy with antimetabolites, the vinca alkaloids and other classes of compounds, it appears that the incidence with these agents is much lower than with alkylators (17).

The drugs most frequently implicated in reports of secondary ANLL are melphalan, chlorambucil, cyclophosphomide, thiotepa, and the nitrosoureas. A particularly high relative risk of secondary ANLL has until now been recorded for patients with multiple myeloma treated with melphalan (44, 47, 54) and for patients with lung cancer treated with busulfan (95). These two cytostatic agents are known to induce an often unpredictable, delayed, and severe marrow toxicity which could be of importance in leukemogenesis. In contrast to this, it has been assumed that treatment with more easily manageable agents, such as cyclophosphamide, is only to a lesser degree followed by leukemia (16, 95).

The development of acute leukemia in patients with nonneoplastic disorders such as rheumatoid arthritis (42) and renal disease was a rare event until these patients began to receive treatment with

cytotoxic immunosuppressive chemotherapy (23, 52, 56, 97). Iatrogenic suppression of immunity with these agents in the course of management of patients with organ homografts is also associated with an increased frequency of malignant neoplasms (17, 69, 81, 98, 102). Recently Louie collected 31 such associations (56). One hundred and nine non-malignant diseases were treated by immunosuppressive drugs, and 94 received no treatment. Acute myelogenous leukemia (AML) or one of its variants was observed in 28 treated patients (25.9%) whereas only 2 developed in the untreated patients (3.2%). This difference was very significant and this high proportion of acute leukemia in treated patients appeared to provide convincing evidence of the leukemogenicity of these agents.

It is known that the immunosuppressant action of these drugs compromises host resistance (70, 68). In these non-neoplastic disorders therapy has usually been given to suppress the production of autoantibodies. The interaction between chronic antigenic stimulation and immunodepression might predispose to malignant change. Suppression of the immunosurveillance system may allow a malignant clone of cells to emerge and multiply (14, 70, 106). This deficiency could also lead to the inability to resist a hypothetical virus-induced leukemia (5).

Primary or secondary immunological deficiency states have been associated with markedly increased incidences of malignancies (68, 25, 102, 106). Patients with primary immunodeficiency disorders such as X-linked agammaglobulinemia (Bruton type), and the DiGeorge syndrome have a sharply increased incidence of malignant neoplasms,

as high as 10,000 times that of the general age-matched population (59, 106). However, the spectrum of malignancies in immunosuppressed patients is qualitatively different from those receiving chronic alkylating agent therapy. Patients with congenital immunodeficiency states develop a variety of malignant conditions but most are lymphoreticular neoplasms, including acute lymphoblastic leukemia (81, 98). Patients who are immunosuppressed with antimetabolites and prednisone following organ transplantation usually develop epithelial carcinomas, (skin, lip, cervix, uterus) and malignant lymphomas; these have an unusual predilection to involve the alimentary tract (17, 70, 68). Except for a rare case report (87), ANLL has not been recognized as a complication of the immunosuppressive therapy given to transplant patients. These differences in the types of malignancies which develop following therapy suggest that complicating ANLL may be due to the known mutagenic actions of the alkylating agents. These observations suggest that the various alkylating agents have much higher leukemogenic potential than other immunosuppressive drugs (17).

Repeated or prolonged episodes of drug-induced marrow dysplasia may produce genetic damage to the hematopoietic stem cell and this may be another possible mechanism which can set the stage for leukemia. Chemical leukemogenesis after exposure to environmental and therapeutic agents has long been recognized. Arsenic, benzene, and toluene have been known to cause acute leukemia in those with a history of heavy exposure (2, 27, 49, 68). The population at high risk includes those involved in the leather and shoe manufacturing, dry cleaning, rotogravure painting, and spray painting. In all cases exposure was

prolonged and heavy and the leukemia was nearly always preceded by a preleukemic syndrome (35). However, bone marrow depression is a more frequent finding in benzene poisoning than is the development of leukemia; the latter arrises in only a small proportion of the affected marrows (104). Chloramphenicol is another agent which frequently produced marrow damage and subsequent acute leukemia (18, 35). These situations are analogous to those seen in post-therapeutic leukemia with alkylating agents where there is evidence of extensive marrow damage prior to the development of leukemia (44, 68, 15, 17). These sequences of pancytopenia followed by leukemia have been described after marrow toxic reactions compounds, as well as after primary aplastic anemia (1, 12, 49).

Patients with chromosomal abnormalities, pancytopenia, myeloproliferative syndromes, and bone marrow dysplasia have been shown to be a great risk of developing acute leukemia (65). The prevalence of this disease in these patients suggests that marrow stem cell injury may be an important factor in the pathogenesis of leukemic transformation. Similar kinds of chromosomal breakage occur spontaneously in congenital disorders such as Down's syndrome (105), Bloom's syndrome, Fanconi's anemia (32), ataxia telangiectasia and other inherited diseases (82, 28). These abnormalities, which are evident in both in vitro and in vivo cellular studies, have led to the speculation that disorganization in genetic material may lead to rearrangements, point mutations, gene deletions, or duplications, at the biochemical level creating the conditions necessary for malignant growth. Similarly, marrow stem cells may be altered or damaged by the

effect of chemotherapy on DNA and on chromosomal karyotypes, eventually leading to the development of leukemia (20, 33).

At least half of all reported cases of ANLL following cytotoxic agent therapy have had documented persistent cytopenia (17). Many of these patients have had documented "pre-leukemia" hypoplastic, hyperplastic, and/or sideroblastic marrows (44, 53). The incidence was evenly distributed among all disease subgroups. The incidence in the literature may actually have been higher since many case reports were brief and did not contain sufficient clinical information (17). Thus, persistent cytopenias and marrow aberrations have emerged as premonitory findings among patients who develop ANLL following prolonged chemotherapy (15, 68).

It is not possible to state at which point in treatment the agent involved becomes leukemogenic. However, since leukemia may develop following continuous chemotherapy with an alkylating agent radiotherapy of various extents, or most commonly, following intensive treatment with extensive irradiation and polychemotherapy, it becomes necessary to develop a way to determine how long to continue therapy after remission, balancing the benefits of treatment against the risk of the development of ANLL.

At present the optimal duration of therapy needed to achieve a chemotherapeutic cure of advanced ovarian carcinoma is unknown. In the past the plan had been to continue chemotherapy in these patients indefinitely even if second look laparotomy procedures were negative (88). However, in view of the therapeutic hazard of leukemia development, the present objectives are directed toward the modification

of alkylating agent therapy and modification of the management of patients receiving this type of therapy. Proposed changes include more frequent use of second look procedures; clonogenic studies of ovarian tumor cells; frequent bone marrow analysis with culture studies; the sequential administration of alkylating agents; and the use of other drugs whenever possible.

Second look procedures include laparoscopy and laparotomy. Second look laparoscopy with cytologic washings and biopsy of visible nodules, followed by second look laparotomy if all results of the laparoscopy are negative, has been advocated. Visible tumor or positive cytologic washings on laparoscopy would indicate continuation of chemotherapy and obviate the need for second look laparotomy, results on laparoscopy would be indications for further surgery before considering discontinuation of effective chemotherapy (71, 78, 107).

The inclusion of in vitro clonogenic assays for predicting the response of tumors to chemotherapy might be useful. This assay is reported to have up to 62% predictive accuracy for complete and partial remission in these patients. This high accuracy rate in predicting clinical drug resistance suggests that it can be used to exclude drug trials which will not be clinically useful for tumor response but which will increase the patients' risk to overall toxicity (3).

Serial bone marrow studies with bone marrow cultures may also help detect the risk of leukemia in these patients (96). However, morphological changes in the marrow are difficult to interpret. Many patients receiving cytotoxic drugs show evidence of dyserythropoiesis

and dysmyelopoiesis, though this usually disappears within a short time of stopping therapy (98). Furthermore, evolution of ANLL is unpredictable, a normal appearing study does not determine future behavior of the marrow. Many patients had normal appearing marrow analysis every few weeks or months before another bone marrow study showed advanced ANLL.

Culturing bone marrow contents would be more indicative of recipient marrow damage, since this results in reduced colony-forming capacity (60). An attempt to monitor bone marrow function by this method would probably provide a good early warning system. At such a preleukemic time, withdrawal of alkylating therapy may allow the marrow to recover.

It may also be possible to obtain good therapeutic results with somewhat less aggressive multi-drug therapy. The vast majority of patients developing ANLL distinctly benefited from therapy, with respect both to clinical remissions and prolongation of life, when compared with untreated patients. Patients with ovarian carcinoma, Hodgkin's disease, and multiple myeloma each accounted for approximately one-third of the cases having autopsy evidence of complete remission from the underlying disease (17). An intermittent schedule would allow time for recovery of both cellular and humoral immune function which had been suppressed by the agent employed and would allow the "rebound-overshoot" phenomenon of immune recovery to occur (39). Moreover, it has been suggested that with continuous chemotherapy one has the risk of suppressing those elements of the immune response necessary for tumor destruction (7, 94).

Another approach may be to substitute antimetabolites and other agents for alkylating agents whenever the choice is equal, since their oncogenic activity is of a lesser degree. With the advent of adriamycin and platinum as effective chemotherapeutic agents in the treatment of ovarian carcinoma, the use of alkylating agents will be decreased (112).

In addition, since immunocompetence of the individual appears to be an important factor in the ultimate prognosis, it has been suggested that the immune response can be spared or even restored during therapy by administering nonspecific immunotherapy, such as BCG (34, 40).

Faced with high numbers of reports of secondary ANLL, the chances of survival from the primary tumor must be weighed against benefit from potential leukemogenic drugs. As in our patients with ovarian carcinoma, the survival curve may only be slightly affected by cases of secondary ANLL.

It is reassuring to know that the incidence of leukemia in patients treated for neoplasms or for non-neoplastic diseases with chemotherapy or combined chemotherapy and radiotherapy is still small and the number of patients enormously benefited by these types of therapy is very large (112). However, an analysis of the use of these drugs in conditions with a more favorable survival rate should take this leukemogenic potential into account. Although the risk of leukemogenesis in man may be small, these drugs should be used with caution in patients with indolent non-neoplastic diseases such as rheumatoid arthritis (17, 92).

Despite the dangers of bone marrow suppression and secondary malignancy, chemotherapy is still the treatment of choice in advanced malignancies. This estimated higher risk of ANLL may be acceptable with treatment of a disease with a relatively poor prognosis if such therapy results in improved survival.

Ultimately, ovarian carcinoma remains a lethal disease with an insidious presentation and, therefore, not easily detectable during its earliest most curable stages. Consequently, the need for aggressive, extensive therapy remains in these patients. With a median survival in untreated cases of less than 10 months, the potential benefits of therapy clearly outweigh the risks. The estimated higher risk of leukemia development may be acceptable in the treatment of a disease with a relatively poor prognosis, if such therapy results in improved survival (76). As is the case with other malignancies, late death from leukemia after prolonged survival of cure from ovarian carcinoma is preferred to early death without remission.

Analysis of the results from large prospective studies in cooperative chemotherapy groups will allow a more precise evaluation of the relative risk of secondary ANLL using single agents or cytostatic drugs in combinations. Long-term follow-up observations of patients in ongoing adjuvant chemotherapy trials should provide a clearer understanding of the risks and benefits of therapy with alkylating agents. Further studies are also needed to evaluate the carcinogenic effects that may result from interactions between different types of treatment, including radiation and alkylating agents (17, 76).

Table 1

CLINICAL STAGING IN CARCINOMA OF THE OVARY

FIGO CLASSIFICATION

STAGE I: Growth limited to the ovaries.

- STAGE IA: Growth limited to one ovary; no ascites.
  - (i) No tumor on the external surface; capsule intact.
  - (ii) Tumor present on the external surface and/or capsule ruptured.

- STAGE IB: Growth limited to both ovaries; no ascites.
  - (i) No tumor on the external surface; capsule intact.
  - (ii) Tumor present on the external surface and/or capsule(s) ruptured.

- STAGE IC: Tumor either Stage IA or Stage IB, but with ascites* present or positive peritoneal washings.

STAGE II: Growth involving one or both ovaries with pelvic extension.

- STAGE IIA: Extension and/or metastases to the uterus and/or tubes.

- STAGE IIB: Extension to other pelvic tissues.

- STAGE IIC: Tumor either Stage IIA or Stage IIB, but with ascites* present or positive peritoneal washings.

STAGE III: Growth involving one or both ovaries with intraperitoneal metastases outside the pelvis and/or positive retroperitoneal nodes. Tumor limited to the true pelvis with histologically proven malignant extension to small bowel or omentum.

STAGE IV: Growth involving one or both ovaries with distant metastases. If pleural effusion is present, there must be positive cytology to allot a case to Stage IV. Parenchymal liver metastases equals Stage IV.

Special Category: Unexplored cases which are thought to be ovarian carcinoma.

*Ascites is peritoneal effusion which in the opinion of the surgeon is pathologic and/or clearly exceeds normal amounts.

Table 2

Number of Patients	dose of uracil mustard (mg)	Patients with ANLL
5	100-500	1
5	500-1,000	1
5	1,000-1,500	0
1	> 1,500	1

Table 3

REPORTED CASES OF ACUTE LEUKEMIA FOLLOWING CHEMOTHERAPY FOR OVARIAN CARCINOMA

Case	Age	Chemo-therapy	Duration of Chemo-therapy	Total Dose	Radiation Therapy	Latent Period	Type of Leukemia	Pancytopenia prior to leukemia	Survival after diagnosis of leukemia	Status of Leukemia/ Ovarian Carcinoma at autopsy or last exam	Ref.
1	NR	No	--	--	Yes	No	?	NR	NR	NR	26
2	44	TT, CTX	21 mo.	110g. 625mg.	9000R-Abd	40 mo.	AML	No	NR	+/-	89
3	70	TT	13 mo.	840mg.	No	30 mo.	AML	17 mo.	few days	+/-	4
4	38	TT, MTX, 5-FU	14 mo.	150mg. 180mg. 17.5g.	No	18 mo.	AML	No	1.5 mo.	+/+	46
5	NR	TT + ?	NR	NR	NR	NR	NR	NR	NR	NR	68
6	54	TT, MTX	48 mo.*	NR	No	87 mo.	AML	24 mo.	1 mo.	+/-	36
7	42	CTX, TT, MTX	48 mo.*	NR	4000R-Pv, 1 course to chest	114mo.	AML	4 mo.	1 mo.	NA;+/-	36
8	32	CLR	86 mo.	NR	No	89 mo.	AML	3 mo.	4 mo.	+/-	90
9	63	TT, CLR	69 mo.	NR	No	73 mo.	AMMOL	No	2 mo.	+/+	92
10	74	TT, CLR	60 mo.	150mg. 7.74g.	No	68 mo.	AML	12 mo.	2 mo.	+/-	38
11	NR	?	NR	NR	?	NR	?	NR	NR	NR	57
12	39	CLR	36 mo.	10g.	No	45 mo.	EL	3 mo.	8 mo.	NA	48
13	68	CLR	40 mo.	6g.	4000R-Pv	60 mo.	EL	No	2 mo.	NA	48
14	48	MEL	NR	NR	Abd, Pv	48 mo.	EL	Yes	10 mo.	+/+	73
15	47	CLR	4 mo.	214mg.	3000R-Abd, 5000R-Pv	33 mo.	AML	2 mo.	10 mo.	+/+	63
16	42	CLR	19 mo.	5.05g.	No	30 mo.	AUL	NR	11 mo.+	alive CR/-	63
17	NR	PAM	18 mo.	NR	No	24 mo.	EL	Yes	7 mo.+	alive +/-	63

Case	Age	Chemo-therapy	Duration of Chemo-therapy	Total Dose	Radiation Therapy	Latent Period	Type of Leukemia	Pancytopenia prior to leukemia	Survival after diagnosis of leukemia	Status of Leukemia/ Ovarian Carcinoma at autopsy or last exam	Ref.
18	NR	TT		NR	No	52 mo.	AML			NA	76
19	NR	UM,5-FU	10-90	NR	4100R-Pv	26 mo.	AML	9 pts	Median	NA	76
20	NR	CTX	mo.	NR	4000R-Pv, ^{32}P	30 mo.	AMMOL	1-9 mo. (median	Survival 1.5 mo.	NA	76
21	NR	PAM		NR	7000R-Abd, Pv	39 mo.	EL	6 mo.) 4pts-NR		+/-	76
22	NR	PAM,CTX, 5-FU		NR	^{32}P	44 mo.	AML			+/+	76
23	NR	PAM		NR	2800R-Pv	39 mo.	AML			+/-	76
24	NR	CLR	10-90	NR	5000R-Pv	44 mo.	AML	9 pts	Median	+/-	76
25	NR	CTX	mo.	NR	No	?	AML	1-9 mo.	Survival	?	76
26	NR	PAM		NR	7000R-Abd, Pv	36 mo.	AML	(median 6 mo.)	1.5 mo.	NA	76
27	NR	PAM,Hexa		NR	?	48 mo.	AML	4pts-NR		+/+	76
28	NR	PAM		NR	?	31 mo.	EL			+/-	76
29	NR	CLR		NR	No	84 mo.	EL			+/-	76
30	NR	CLR		NR	No	90 mo.	AML			+/-	76
31	51	TT	30 mo.	150mg	4500R-Pv	44 mo.	AML	10 mo.	3 weeks	+/-	43
32	68	MEL,CTX	16 mo.		No	46 mo.	AML	No	few weeks	+/-	24
33	52	MEL	48 mo.	1580mg	No	58 mo.	AML	No	1 mo.	+/+	24
34	65	MEL	61 mo.	1140mg	No	77 mo.	AML	No	2 mo.	+/-	24
35	45	MEL	34 mo.	1030mg	4000R-Abd	36 mo.	EL	NR	2 mo.	+/+	24
36	50	MEL	15 mo.	310mg	2800R-Abd, 5820R-Pv	19 mo.	AMMOL	Yes	NR	NR	85
37	33	MEL	NR	NR	Yes	33 mo.	AML	Yes	NR	NR	112
38	66	No	--	--	1000R	90 mo.	AML	Yes	1 mo.	NA	112
39	40	UM,5-FU	NR	NR	5200R, radium	60 mo.	AMMOL	Yes	7 mo.	-/-	112
40	43	UM,5-FU	NR	NR	3800R	84 mo.	AMMOL	Yes	6 mo.	-/-	112

Case	Age	Chemo-therapy	Duration of Chemo-therapy	Total Dose	Radiation Therapy	Latent Period	Type of Leukemia	Pancytopenia prior to leukemia	Survival after diagnosis of leukemia	Status of Leukemia/ Ovarian Carcinoma at autopsy or last exam	Ref.
41	49	TT,CTX	NR	NR	No	96 mo.	AMMOL	Yes	0.4 mo.	NA	112
42	56	CLR	NR	NR	Yes	36 mo.	MPS,EL	Yes	14 mo.	+/-	112
43	67	MEL	32 mo.	NR	No	54 mo.	AMMOL	No	few days	NR	66
44	39	TSF	36 mo.	413g	No	51 mo.	?	1 mo.	2 mo.	+/-	67
45	66	TSF	25.5 mo.	246g	No	53 mo.	AML	1 mo.	1 mo.	+/-	67
46	65	TSF	5.5 mo.	126g	Method of McWhirter	21 mo.	AML	5 mo.	2 mo.	+/+	67
47	52	TSF	36 mo.	686g	No	56 mo.	?	12 mo.+	6 mo.	+/-	67
48	70	TSF	37 mo.	365g	No	48 mo.	?	11 mo.	2 mo.+	alive+/-	67
49	45	TSF	11 mo.	186g	No	48 mo.	?	36 mo.	1 mo.+	alive+/-	67
50	65	TSF	31 mo.	239g	No	58 mo.	?	26 mo.	1 mo.	+/-	67
51	58	TSF	19 mo.	161g	5000R-Pv	31 mo.	?	20 mo.	1 mo.+	alive+/-	67
52	48	UM,5-FU	33 mo.	900mg, 71g	4000R,Abd, Pv,radium	50 mo.	AML	?	7 mo.	+/-	Present Cases
53	43	UM,5-FU	62 mo.	1700mg, 85.8g	3800R-Abd, Pv	79 mo.	AMMOL	?	7 mo.	NA; +/-	
54	51	UM,5-FU	32 mo.	348mg, 24g	3875R-Abd, Pv	86 mo.	MDS,AML, AMMOL	1 mo.	5 mo.	NA; +/-	

Abbreviations: TT=thiotepa; CTX=cyclophosphamide; MTX=methotrexate; CLR=chlorambucil; MEL=melphalan; PAM=phenylalanine mustard; Hexa=hexamethylmelamine; TSF=treosulfan; AL=acute leukemia; AML=acute myelocytic leukemia; AMMOL=acute myelomonocytic leukemia; EL=erythroleukemia; ANL=acute undifferentiated leukemia; MDS=myelodysplastic syndrome; Abd=abdomen; Pv=pelvis
NA=no autopsy; NR=not reported

Latent period=interval from beginning of chemotherapy to diagnosis of leukemia

*=intermittent

Table 4

Ref.	Total # of patients	Long-term survivors	# with ANLL	% of total	% of long-term survivors	Length of survival (yrs.)
36	400	14	2	0.50	14.28	5
76	5455	NR	13	0.76	-----	2
43	374	10	1	2.00	10.00	3
24	474	48	4	0.84	8.33	3
67	553	NR	7	1.30	-----	7 > 3 1 > 2
present cases	79	16	3	3.75	18.75	5

REFERENCES

1. Aksoy, M., Dincol, K., Erdem, S., and Dincol, G.: Acute leukemia due to chronic exposure to benzene. Am. J. Med., 52:160, 1972.

2. Aksoy, M., Erdem, S., and Dincol, G.: Leukemia in shoe-workers exposed chronically to benzene. Blood, 44:837, 1974.

3. Alberts, D.S., Samon, S.E., Chen, H.S., Surwit, E.A., Soehlen, B., Young, L., and Moon, T.E.: In-vitro clonogenic assay for predicting response of ovarian cancer to chemotherapy. Lancet, 2:340, 1980.

4. Allan, W.S.: Acute myeloid leukemia after treatment with cytostatic agents. Lancet, 2:775, 1970.

5. Allison, A.C.: Cancer in immunosuppressed experimental animal and human patients. Johns Hopkins Med. J., 3 (Suppl): 341, 1974.

6. Auclerc, G., Jacquillat, C., Auclerc, M.F., Weil, M., and Bernard, J.: Post-therapeutic acute leukemia. Cancer, 44:2017, 1979.

7. Bagshawe, K.D.: Manipulation of the immune mechanism in the treatment of cancer in present status and future possibilities in immunology and cancer. Univ. Ottawa Press, Ottawa, 1973, p. 111.

8. Bizzozero, O.J., Johnson, K.G., and Ciocco, A.: Radiation-related leukemia in Hiroshima and Nagasaki, 1946-1964. I. Distribution, incidence and appearance time. N. Engl. J. Med., 274:1095, 1966.

9. Bizzozero, O.J., Jr., Johnson, K.G., Ciocco, A., Rawasaki, S., and Toyoda, S.: Radiation-related leukemia in Hiroshima and Nagasaki, 1946-1964. II. Observations on type-specific leukemia, survivorship and clinical behavior. Ann. Intern. Med., 66:522, 1967.

10. Bloom, A.D., and Tjio, J.H.: In vivo effects of diagnostic X-irradiation on human chromosomes. N. Engl. J. Med., 270:1341, 1964.

11. Booth, B.A., and Sartorelli, A.C.: Growth inhibition of a spectrum of transplanted mouse tumors by combinations of inhibitors of nucleic acid biosynthesis and alkylating agents. Cancer Res., 23:1762, 1963.

12. Brauer, M.J., and Damashek, W.: Hypoplastic anemia and myeloblastic leukemia following chloramphenicol therapy. N. Engl. J. Med., 277: 1003, 1967.

12A. Branschwig, A., and Clark, D.G.: Intestinal surgery for advanced cancer of the ovary in ovarian cancer, Springer-Verlag, New York, 1968, p. 165.

13. Buckton, R.E., Jacobs, P.A., Court Brown, W.M. and Doll, R.: A study of the chromosome damage persisting after X-ray therapy for ankylosing spondylitis. Lancet, 2:676, 1962.

14. Burnet, F.M.: Immunological aspects of malignant disease. Lancet, 1:1171, 1967.

15. Cadman, E.C., Capizzi, R.L., and Bertino, J.R.: Acute nonlymphocytic leukemia. A delayed complication of Hodgkin's disease therapy: analysis of 109 cases. Cancer, 40:1280, 1977.

16. Cameron, S.: Chlorambucil and leukemia. N. Engl. J. Med., 296:1065, 1977.

17. Casciato, D.A., and Scott, J.L.: Acute leukemia following prolonged cytotoxic agent therapy. Medicine, 58:32, 1979.

18. Cohen, H.J. and Huang, A.T.F.: A marker chromosome abnormality: occurrence in chloramphenicol associated acute leukemia. Arch. Intern. Med., 123:440, 1973.

19. Cohen, R.J., Wiernik, P.H., and Walker, M.D.: ANLL associated with nitrosourea chemotherapy: Report of two cases. Cancer Treat. Rep., 60:1257, 1976.

20. Colburn, N.H. and Boutwell, R.K.: The binding of beta-propriolactone and some related alkylating agents to DNA, RNA, and protein initiating power of alkylating agents and their binding to DNA. Cancer Res., 28:653, 1968.

21. Court Brown, W.M., and Doll, R.: Mortality from cancer and other causes after radiotherapy for ankylosing spondylitis. Br. Med. J., 1:1327, 1965.

22. Davis, H.L., Jr., Prout, M.N., McKenna, P.J., Cole, D.R., and Korbitz, B.C.: Acute leukemia complicating metastatic breast cancer. Cancer, 31:543, 1973.

23. DeBock, R.F. and Peetermans, M.G.: Leukemia after prolonged use of melphalan for non-malignant disease. Lancet, 1:1208, 1977.

24. Einhorn, N.: Acute leukemia after chemotherapy (melphalan). Cancer, 41:444, 1978.

25. Fahey, J.L.: Cancer in the immunosuppressed patient. Ann. Intern. Med., 75:310, 1971.

26. Farber, M., and Borum, K.: Leukemia and malignant tumour in the same patient. Brit. J. Haemat., 8:313, 1962.

27. Forni, A., and Vigliani, E.C.: Chemical leukemogenesis in man. Series Haematol., 7:211, 1974.

28. Fraumeni, J.F., Jr.: Clinical epidemiology of leukemia. Sem. in Hematol., 6(3):250, 1969.

29. Fraumeni, J.F., Jr., and Miller, R.W.: Editorial: Drug-induced cancer. J. Natl. Cancer Inst., 48:1267, 1972.

30. Fraumeni, J.F., Jr., and Miller, R.W.: Epidemiology of human leukemia: Recent observation. J. Nat'l. Cancer Inst., 38:593, 1967.

31. Garfield, D.H.: Letter: Acute erythromegakaryocytic leukemia after treatment with cytostatic agents. Lancet 2:1037, 1970.

32. Garriga, S., and Crosby, W.H.: The incidence of leukemia in families of patients with hypoplasia of the marrow. Blood, 14:1008, 1959.

33. Gebhart, E.: Chromosome aberrations induced by myeleran in human leukocytes _in vitro_. Humangenetik, 7:126, 1969.

34. George, R.P., Poth, J.L., Gordon, D., and Schrier, S.L.: Multiple myeloma: Intermittent combination chemotherapy compared to continuous therapy. Cancer, 29:1665, 1972.

35. Goguel, A., Cavigneaux, A., and Bernard, J.: Les leucemies benzeniques. Bulletin INSERM, 22:421, 1967.

36. Greenspan, E.M., and Tung, B.G.: Acute myeloblastic leukemia after cure of ovarian cancer. J.A.M.A., 230:418, 1974.

37. Hale, W.M., and Stover, R.D.: Effects of ionizing radiation on immunity. Radiation Res., 1:459, 1954.

38. Haque, T., Lutcher, C., Faguet, G., and Talledo, O.: Chemotherapy-associated acute myelogenous leukemia and ovarian carcinoma. Am. J. Med. Sci. 272(2):225, 1976.

39. Harris, J., Sengar, D., Stewart, T., and Hyslop, D.: The effect of immunosuppressive chemotherapy on immune function in patients with malignant disease. Cancer, 37:1058, 1976.

40. Hersh, E.M., Gutterman, J.V., Mauligit, G., McCredie, K.B., Boley, G.P., Frenceich, E.J., Rossen, R.D., and Butler, W.T.: Host defense, chemical immunosuppression and the transplant recipient - Relative effects of intermittent versus continuous immunosuppressive therapy with reference to the objectives of treatment. Transplant Proc., 5:1191, 1973.

41. Hoover, R., and Fraumeni, J.F. Jr.: Risk of cancer in renal transplant recipients. Lancet, 2:55, 1973.

42. Kapadia, S.B., and Kaplan, S.S.: Acute myelogenous leukemia following immunosuppressive therapy for rheumatoid arthritis. Am. J. Clin. Path., 70:301, 1978.

43. Kapadia, S.B., and Krause, J.R.: Ovarian carcinoma terminating in acute nonlymphocytic leukemia following alkylating agent therapy. Cancer, 41:1676, 1978.

44. Karchmer, R.K., Amare, M., Larsen, W.E., Mallouk, A.G., and Caldwell, G.G.: Alkylating agents as leukemogens in multiple myeloma. Cancer, 33:1103, 1974.

45. Karchmer, R.K., Caldwell, G.G., and Chin, T.D.: Acute leukemia following irradiation for carcinoma of the larynx. Blood, 43:721, 1974.

46. Kaslow, R.A., Wisch, N., and Glass, J.L.: Acute leukemia following cytotoxic chemotherapy. J.A.M.A., 219:75, 1972.

47. Khaleeli, M., Keane, W.M., and Lee, G.R.: Sideroblastic anemia in multiple myeloma: A preleukemia change. Blood, 41:17, 1973.

48. Khandekar, J.D., Kurtides, S.E., and Stalzer, R.: Acute erythroleukemia complicating prolonged chemotherapy for ovarian carcinoma. Arch. Intern. Med., 137:355, 1977.

49. Kjeldsberg, C.R., and Ward, H.P.: Leukemia in arsenic poisoning. Ann. Intern. Med., 77:935, 1972.

50. Kleinknecht, C., Guesry, P., Lenoir, G., and Broyer, M.: High-cost benefit of chlorambucilin frequently relapsing nephrosis. N. Engl. J. Med., 296-48, 1977.

51. Kong-oo, G.: Total body irradiation and human chromosomes: Cytogenetic studies of the peripheral blood and bone marrow leukocytes seen years after total-body irradiation. Radiation Research, 35:155, 1968.

52. Kuis, W., Dekraker, J., and Kuijten, R.H., et al: Acute nephrotic syndrome with immunosuppressive drugs. Helr. Paediat. Acta., 31:91, 1976.

53. Kyle, R.A., Pierre, R.V., and Bayrd, E.D.: Multiple myeloma and acute leukemia associated with alkylating agents. Arch. Intern. Med., 135:185, 1975.

54. Kyle, R.A., Pierre, R.V., and Bayrd, E.D.: Multiple myelomonocytic leukemia. N. Engl. J. Med., 283:1121, 1970.

55. Li, F.P., Jaffe, M., and Cassidy, V.R.: Risk of secondary tumors in survivors of childhood cancer, in Proceedings of the 65th Annual Meeting of the American Association for Cancer Research and the 10th Annual Meeting of the American Society of Clinical Oncologists, Houston, March 14, 1974. Baltimore, Williams and Wilkins, Co., 1974, p. 170.

56. Louie, S., and Schwartz, R.S.: Immunodeficiency and the pathogenesis of lymphoma and leukemia. Semin. Aematol., 15:117, 1978.

57. McKenna, R.W., Bloomfield, C.D., Bowers, T., and Branning, R.: Treatment associated acute nonlymphocytic leukemia (ANLL): The morphologic pattern. Proc. Am. Assoc. Cancer Res., 18:222, 1977.

58. Millard, R.E.: Abnormalities of human chromosomes following therapeutic radiation. Cytogenetics, 4:277, 1965.

59. Miller, R.W.: Persons with exceptionally high risk of leukemia. Cancer Res., 27:2420, 1967.

60. Milner, G.R., Testa, N.G., Dexter, T.M., Muldal, S., MacIver, J.E., and Lajtha, L.G.: Bone marrow culture studies in refractory cytopenia and "smouldering leukemia". Brit. J. Haemat. 35:251, 1977.

61. Modan, B., and Lilienfeld, A.: Polycythemia vera and leukemia - The role of radiation treatment: A study of 1222 patients. Medicine (Baltimore), 44:305, 1965.

62. Moloney, W.C.: Leukemia in survivors of atomic bombing. N. Engl. J. Med., 253:88, 1955.

63. Morrison, J., and Yon, J.L.: Acute leukemia following chlorambucil therapy for advanced ovarian and fallopian tube carcinoma. Gynecol. Oncol., 6:115, 1978.

64. Murray, R., Heckel, P., and Hempelmann, L.: Leukemia in children exposed to ionizing radiation. N. Engl. J. Med., 261:585, 1959.

65. Nowell, P.C.: Marrow chromosome studies in "preleukemia" - Further correlation with clinical course. Cancer, 28:513, 1971.

66. Ortonne, J.P., Thivolet, J., Chouvet, B., and Coiffet, J.: Pyoderma gangrenosum, cystadeno-carcinome ovarian traite's par melphalan et leucemre aique myeloblastique. Ann. Dermatol. Venereol. (Paris), 106:251, 1979.

67. Pedersen-Bjergaard, J., Nissen, N., Sorensen, H., Hou-Jensen, K., Larsen, M., Ernst, P., Ersbol, J., Knudtzon, S., and Rose, C.: Acute non-lymphocytic leukemia in patients with ovarian carcinoma following long-term treatment with treosulfan (=dihydroxybusulfan). Cancer, 45:19, 1980.

68. Penn, I.: Development of cancer as a complication of clinical transplantation. Transplant Proc., 9:1121, 1977.

69. Penn, I.: Development of cancer as a complication of clinical transplantation. Transplantation Proc., 9:1121, 1977.

70. Penn, I.: Occurrence of cancer in immune deficiencies. Cancer, 34:858, 1974.

71. Piver, M.S., Lele, S., Barlow, J., and Gamarra, M.: Second-look laparotomy. Obstet. Gynecol., 55:571, 1980.

72. Poth, J.L., Georrie, R.P., Creger, W.P., and Schrier, S.L.: Acute myelogenous leukemia following localized radiotherapy. Arch. Intern. Med., 128:802, 1971.

73. Preisler, H.D., and Lyman, G.H.: Acute myelogenous leukemia subsequent to therapy for a different neoplasm: Clinical features and response to therapy. Am. J. Hematol., 3:209, 1977.

74. Prejean, J.D., Griswold, D.P., Peckham, J.C., Casey, A.E., Weisburger, E.K., and Weisburger, J.H.: Carcinogenicity of clinically used anticancer drugs. Proc. Am. Assoc. Cancer Res., 14:79, 1973.

75. Puri, H.C., and Campbell, R.A.: Cyclophosphamide and malignancy. Lancet, 1:1306, 1977.

76. Reimer, R.R., Hoover, R., Fraumeni, J.F., Jr., and Young, C.: Acute leukemia after alkylating agent therapy of ovarian cancer. N. Engl. J. Med., 297:177, 1977.

77. Roberts, M.M., and Bell, R.: Acute leukemia after immuno-suppressive therapy. Lancet, 2:768, 1976.

78. Rosenoff, S.H. and Young, R.C.: Peritoneoscopy: A valuable staging tool in ovarian carcinoma. Ann. Intern. Med., 83:37, 1975.

79. Rosner, F., and Grunwald, H.W.: Cytotoxic drugs, and leukemo-genesis. Clin. Haematol., 9(3):663, 1980.

80. Rosner, F., and Grunwald, H.: Hodgkin's disease and acute leukemia. Am. J. Med., 58:339, 1975.

81. Rosner, F., and Grunwald, H.: Multiple myeloma terminating in acute leukemia. Am. J. Med., 57:927, 1974.

82. Schroeder, T.M., and Kurth, R.: Spontaneous chromosomal breakage and high incidence of leukemia in inherited disease. Blood, 37:96, 1971.

83. Schwartz, A.D., Lee, H., and Baum, E.S.: Leukemia in children with Wilm's tumor. J. Pediatr., 87:374, 1975.

84. Sharpe, H.B.: Observations on the effect of therapy with nitrogen mustard or a derivative on chromosomes of human peripheral blood lymphocytes. Cell. Tissue Kinet., 4:501, 1971.

85. Shetty, M.R., and Freel, R.: Therapy-linked leukemia: A case report. Gynecol. Oncol., 7:264, 1979.

86. Sieber, S.M., and Adamson, R.H.: Toxicity of antineoplastic agents in man: chromosomal aberrations, antifertility effects, congenital malformations and carcinogenic potential. Adv. Cancer Res., 22:57, 1975.

87. Silvergleid, A.J., and Schrier, S.L.: Acute myelogenous leukemia in two patients treated with azathioprine for nonmalignant diseases. Am. J. Med., 57:885, 1974.

88. Simpson, C.L., Hempslmann, L.H., and Fuller, L.M.: Neoplasia in children treated with X-rays in infancy. Radiology, 64:840, 1965.

89. Smit, C.G.S., and Meyler, L.: Acute myeloid leukemia after treatment with cytostatic agents. Lancet, 2:671, 1970.

90. Smith, P.G.: Leukemia and other cancers following radiation treatment of pelvic disease. Cancer, 39:1901, 1977.

91. Solomon, R.B., and Firat, D.: Acute leukemia following treatment with irradiation and alkylating agent. N.Y. State J. Med., 71:2422, 1971.

92. Sotrel, G., Jafari, K., Lash, A., and Stepto, R.: Acute leukemia in advanced ovarian carcinoma after treatment with alkylating agents. Obstet. Gynecol., 47(supplement):675, 1976.

93. Steinberg, A.A., Plotz, P.H., Wolft, S.M., Wong, V.G., Agus, S.G., and Decker, J.L.: Cytotoxic drugs in treatment of non-malignant diseases. Ann. Intern. Med., 76:619, 1972.

94. Stewart, T.H., Klaassen, D., and Crook, A.F.: Methotrexate in the treatment of malignant tumors - Evidence for the possible participation of host defense mechanisms. Canad. Med. J., 101:191, 1969.

95. Stott, H., Fox, W., Girling, D.J., Stephens, R.J., and Galton, D.A.G.: Acute leukemia after busulfan. Br. Med. J., 2:1513, 1977.

96. Sultan, C.: In discussion following: Tchernia, G., Mielot, F., Subtil, E., and Parmentier, C.: Acute myeloblastic leukemia after immunodepressive therapy for primary nonmalignant disease. Blood Cells, 2:67, 1976.

97. Tchernia, G., Mielot, F., Subtil, E., and Parmentier, C.: Acute myeloblastic leukemia after immunodepressive therapy for primary nonmalignant disease. Blood Cells, 2:67, 1976.

98. Therapy-linked leukemia. Lancet., 1:519, 1977.

99. Third National Cancer Survey, Advanced Three-Year Report, 1969-1971 Incidence. Biometry Branch, National Cancer Institute, National Institutes of Health, Bethesda, MD, 1974, p. 13.

100. Tulliez, M., Richard, M.F., Jan, F., and Sultan, C.: Preleukemic abnormal myelopoiesis induced by chlorambucil: A case study. Scand. J. Haematol., 13:179, 1974.

101. Ulrich, H.: Incidence of leukemia in radiologists. N. Engl. J. Med., 234:45, 1946.

102. Urano, Y., Taguchi, T., Schimamine, T., and Takayasu, H.: Leucimieaigue myeloblastique 8 ans apres alloqreffe renale. Nouv. Presse Med., 7:371, 1978.

103. Videback, A.: Leukemia and cancer in relation to immunosuppressive therapy. Scand. J. Haematol., 10:241, 1973.

104. Vigliani, E.C., and Saita, G.: Benzene and Leukemia. N. Engl. J. Med., 271:872, 1964.

104A. Wade, M.E., and Williams, H.M.: Combination chemotherapy in clinical practice: Recent application to gynecologic cancers. Conn. Med., 31:426, 1967.

105. Wald, N., Borges, N.H., Li, C.C., Turner, J.H., and Harnois, M.C.: Leukemia associated with monogolism. Lancet, 1:1228, 1961.

106. Waldmann, T.A., Strober, W., and Blaese, R.M.: Immunodeficiency disease and malignancy. Ann. Intern. Med., 77:605, 1972.

107. Wallach, R.C., and Blinick, G.: The second look operation for carcinoma of the ovary. Surg. Gynecol. Obstets., 131:1085, 1970.

108. Walpose, A.L.: Carcinogenic action of alkylating agents. Ann. N.Y. Acad. Sci., 68:750, 1958.

109. Wantzin, G.L., and Jensen, M.K.: The induction of chromosome abnormalities by melphalan in rat bone marrow cells. Scand. J. Haematol., 11:135, 1973.

110. Weinfeld, A., Westin, J., Ridell, B., and Swolin, B.: Polycythemia vera terminating in acute leukemia. Scand. J. Haematol., 19:255, 1977.

111. Westberg, N.G., and Swolin, B.: Acute myeloid leukemia appearing in two patients after prolonged continuous chlorambucil treatment for Wegener's granulomatosis. Acta Med. Scand., 199:373, 1976.

112. Zarrabi, M.H., and Rosner, F.: Acute myeloblastic leukemia following treatment for non-hematopoietic cancers: Report of 17 cases and review of the literature. Am. J. Hematol., 7:357. 1979.

Ernest Kohorn F 322. 10 12 84

~~Alan Pratt~~